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Thomas M. Boyce
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Beutler, et al.

Serial No.: 09/396,985

Filed: September 15, 1999

For: LPS-RESPONSE GENE COMPOSITIONS
AND METHODS

Group Art Unit: 1646

Examiner: Basi, N.

Atty. Dkt. No.: UTSD:602/TMB

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SUPPLEMENTAL RESPONSE TO OFFICE ACTION MAILED APRIL 23, 2002

AND

DECLARATION OF DAVID D. CHAPLIN, M.D., PH.D.

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants respectfully submit a Supplemental Response under 37 C.F.R. 1.111 (2) to the Official Action mailed April 23, 2002 (the "Action"). This Supplemental Response provides a declaration of David D. Chaplin, M.D., Ph.D. in support of Applicants' arguments in response along with Applicants' comments. No amendments are presented. This Supplemental Response is filing within the six month statutory period for a response. A response to the Action was filed

September 23, 2002 accompanied by a request for a two-month extension of time to respond. No fee is believed due in respect of the present filing. However, should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/UTSD:602. Reconsideration of the application is respectfully requested.

I. SUPPLEMENTAL RESPONSE TO OFFICE ACTION

A. The Claims are Definite Under 35 U.S.C. § 112, Second Paragraph

Claims 38-40, 52-61, 63-68, 70-75, and 100 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse this rejection.

i) The name TLR-4 is an art accepted term and definite in its meaning in light of the specification.

The Action maintains the rejection of claims 38, 40, 52, 55, 56, and 63-64 on the grounds that “the art nor specification disclose the structural and functional properties which must be present for the polypeptide to be classified as a TLR-4 polypeptide.” The Action at page 2, lines 12-13 and page 4, lines 7-8. The Action also concludes that since name of TLR-4 has changed once in the literature such changes render the use of the term TLR-4 indefinite. The Action at pages 2-3 and page 4, paragraph 3. The Action further notes that proteins of a different name may exist that share the same structure and properties as that named as TLR-4. Applicants respectfully traverse.

A proper evaluation of the claims under the second paragraph of 35 U.S.C. § 112 requires that the claims be read in light of the specification as interpreted by one of ordinary skill in the

art. *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1579, 28 USPQ2d 1333, 1339 (Fed. Cir. 1993); *In re Moore*, 439 F.2d 1232, 1235 (C.C.P.A. 1971).

In support of Applicants' argument, Applicants provide a declaration of Dr. David D. Chaplin, a skilled artisan in the field of endotoxins and cellular biology. As set forth in paragraph 8 of the declaration, Dr. Chaplin points out that the application provides at least sufficient structural and functional properties by which to identify a protein as TLR-4 or its homolog. Further, Dr. Chaplin states that the particular name associated with TLR-4 and its homologs is not determinative of their identity. Rather, it is their structure, primarily the similarity of the amino acid sequences among members of the TLR-4 family, and their function, primarily their role in mediating responses to endotoxins, that identifies TLR-4 polypeptides. Further support of the Applicants' argument is found in paragraph 9 of the declaration of Dr. Chaplin which states that the family of TLR-4 receptors share high sequence similarities in specific domains, identifiable by their shared sequence motifs, as provided by the application. See, for example, pages 110-122. Paragraph 10 of the declaration of Dr. Chaplin provides further support for the Applicants' argument in that it points out that the domains of TLR-4 have specific functions, as described in the application. Primarily, TLR-4 polypeptides act to signal the presence of LPS. TLR-4 is an essential component of the signaling process and its ability to so signal is one of its defining functions. In paragraph 11 of the declaration, Dr. Chaplin further states that researchers in the field of LPS signaling are well aware of the remaining members of the toll-like receptor family, generally, and are able to identify TLR-4 and its homologs using the structural and functional features shared by all TLR-4 polypeptides.

Applicants respectfully point out that the law does not require that the Applicants define in the specification every term of art well known to the artisan. Use of a well known term of art

in the specification without detailed definitions thereof does not render claims utilizing that same language indefinite. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556-58, 220 USPQ 303, 315-16 (Fed. Cir. 1983). Claims may therefore make use of the language understood by those of skill in the art without additional, detailed definitions in the written description. *Id.* Where later developed terms are arguably more definite than the terms available near the filing date, later accepted and more precise terms are favored. *In re Fisher*, 427 F.2d 833, 838 (C.C.P.A. 1970). The name TLR-4 is in common use among artisans in the field in exactly the sense in which the Applicants have defined it.

Applicants respectfully submit, that in view of the above, one of ordinary skill in the art would find the language of the claims definite in light of the specification. Applicants therefore respectfully submit that claims 38-40, 52-68, 70-75 are not indefinite under the second paragraph of 35 U.S.C. § 112 and request that the rejection be withdrawn.

ii) Lipopolysaccharide mediated responses are clear and well known to those of skill in the art.

Claims 52 and 101-103 are rejected on the grounds that they are indefinite because the phrase “mediation of the lipopolysaccharide mediated response” is allegedly not clear. Claims 38, 40 and 52 are rejected because the phrase “liposaccharide mediated response” is allegedly unclear. The Action queries “where does the lipopolysaccharide pathway begin and end?” The Action, page 3, lines 11-12. Applicants respectfully traverse.

In response to the previous argument in rejection, Applicants have referred to the specification at page 2, line 14 through page 4, line 24, and especially page 22 lines 3-7 for a succinct description of the events and circumstances that comprise the initiation of a response to LPS and the resultant responses. Further, exemplary parameters and methods for measuring and determining the response are found in several locations in the specification: page 87, line 5

through page 88, line 15, Example 2 (page 95, line 25 through page 96, line 18), and Example 9 (page 123, line 1 through page 129, line 20).

In the section of the Specification titled “Assays for LPS responsiveness” two examples of LPS-mediated response assays are described: a splenocyte proliferation assay and a macrophage response assay. See the specification at page 87, line 8 to page 88, line 15. The splenocyte response assay compares the proliferation of splenocytes incorporating tritiated thymidine (as measured by counts per minute, CPM) with and without stimulation with LPS. The macrophage response assay measures the percent of cytotoxicity due to TNF released by cells in response to LPS. In yet another means of assaying for LPS response, TNF production may be directly measured. See the specification at page 3, lines 7-13, FIG. 15C, and page 87, line 23 through page 88, line 7.

These are exemplary parameters and methods for measuring the LPS response. The specification thereby provides concrete examples, methods, and standards for measuring responses to LPS endotoxin mediated through TLR-4.

The Applicants' argument is further supported in the declaration of Dr. David Chaplin. Paragraph 5 of the declaration of Dr. Chaplin states that the specification clearly sets forth the actors and elements of lipopolysaccharide mediated responses that are mediated by TLR-4. For example, see pages 87-88, which refer to TNF production and splenocyte proliferation assays, commonly employed assays for LPS response. Paragraph 6 of the declaration of Dr. Chaplin further states that a skilled researcher in endotoxin biology, relying upon the generally available knowledge in the field, would understand that in the context of the application the “lipopolysaccharide pathway” is the cellular response mounted by the action of lipopolysaccharide endotoxins mediated by TLR-4. As disclosed in the specification and as

known to the researcher in the field, one may measure such responses through a variety of means, each identifying and measuring responses at a particular point in the signaling pathway.

Additional methods and parameters are available to the ordinary artisan through the knowledge of one of skill in the art. Applicants respectfully reiterate that the law does not require that the Applicants define in the specification every term of art well known to the artisan. Use of a well known term of art in the specification without detailed definitions thereof does not render claims utilizing that same language indefinite. *W.L. Gore & Assoc., Inc.* 721 F.2d 1540, 1556-58.

Applicants respectfully submit that the claims are definite under the second paragraph of 35 U.S.C. § 112 when properly viewed in light of the ordinary skill of one in the relevant art and the detailed descriptions available to the artisan in the applicants specification. Applicants therefore respectfully request that the rejections be withdrawn.

iii) Summary

Applicants respectfully submit that claims 38, 40, 52, 55, 56, 62-64 and the claims depending upon them are not indefinite under 35 U.S.C. § 112, second paragraph. Applicants respectfully request withdrawal of the rejections.

B. The Pending Claims are Enabled.

The Action rejects claims 38-40, 52-61, 63-68, 70-75 and 100-103 under the first paragraph of 35 U.S.C. § 112. The Action alleges that the only screening method enabled is that which results in the altered expression of TLR-4 of SEQ ID NOS: 2, 4, 6, 98, or 99. Therefore, the Action concludes, methods of screening for modulators of LPS mediated responses through their interaction with TLR-4 are not enabled. Applicants respectfully traverse.

The pending claims are directed to methods of screening for modulators of a lipopolysaccharide mediated response that compare the response before and after contact of TLR-4 with a putative modulator or candidate substance. Altered expression of TLR-4 of SEQ ID NOS: 2, 4, 6, 98, or 99 may be *one* mode of LPS response that is measured, but it is not the sole means of measuring TLR-4 mediated LPS responses disclosed by the specification.

Further support of Applicants' argument is provided in the declaration of Dr. David D. Chaplin, in paragraphs 13-14. Paragraph 13 of the declaration of Dr. Chaplin states that it is well within the skill of one in the field of endotoxin and cellular biology to screen for compounds that modulate the LPS responses through their action upon TLR-4 beyond up or down regulation of TLR-4 expression. The screening of candidate compounds for their effects upon protein action and interaction is routine in the field. In view of the contents of the application, such screening is not limited to those compounds that may alter TLR-4 expression. Indeed, the general expectation of researchers performing such screens is that they will produce small compounds that specifically alter the binding specificity, signaling capacity, or other functional property of the target protein, in this case, TLR-4. Paragraph 14 of the declaration of Dr. Chaplin further states that the specification clearly sets forth assays of TLR-4 activity in the LPS response pathway that can be used by one of ordinary skill in the art to determine, without undue experimentation, whether or not such candidate compounds modulate the action of TLR-4 independently of any action upon TLR-4 expression. For example, such assays are described in the specification at pages 87-88. Furthermore, these and further assays are available through the general knowledge of one of skill in the field of endotoxin biology.

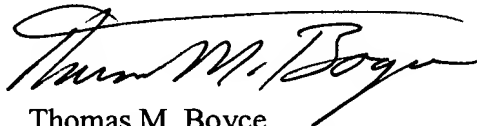
In view of the disclosure provided in the specification and the clarification provided above, Applicants respectfully submit that the claims are enabled and that the rejection be withdrawn.

C. Conclusion

Applicants have submitted factual evidence in the form of Dr. Chaplin's declaration and remarks which are believed to place the present claims in condition for allowance. In view of this, Applicants respectfully request that the present claims be passed for allowance. Should the Examiner have any comments or questions with regard to any statements contained herein, or any suggestions as to claim modification, the Examiner is respectfully requested to contact the Applicants' representative listed below.

Please date-stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,



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